CONFIDENTIAL

Attorney Docket No: NAVI-009/02US **PATENT**

DECLARATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

the specification of which:

[X] is attached hereto.

[] was filed on , and identified as Attorney Docket No. NAVI-009/02US.

[] was filed on , as Application Serial No. .

and

[] the amendment(s) of which were filed on .

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) (Country) (Number) (Day/Month/Year Filed)	Priority Claimed (Yes/No)
, ,	Yes
, ,	Yes

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

60/100,290	September 14, 1998
(Application Number)	(Filing Date)
60/100,224	September 14, 1998
(Application Number)	(Filing Date)
60/109,232	November 18, 1998
(Application Number)	(Filing Date)
60/109,234	November 18, 1998
(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Appl. Ser. No.	Filing Date	Status (Pat'd./Pend./Aband.)

I direct that correspondence concerning this application be directed to

COOLEY GODWARD LLP
Attention: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, California 94306-2155
Telephone (650) 843-5000.
Facsimile (650) 857-0663

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

361809 v1/PA
7R6901!.DOC

Full name of sole or First inventor: Grass, George M.

Inventor's signature ______________________ Date 5/6/99

Residence: Tahoe City, California

Citizen of: United States of America

Post Office Address: 1506 Juniper Mountain Road, P.O. Box 1242
Tahoe City, California 96145

Full name of sole or Second inventor: Leesman, Glen D.

Inventor's signature ______________________ Date 05/10/99

Residence: Hamilton, Montana

Citizen of: United States of America

Post Office Address: 186 Nighthawk Lane
Hamilton, Montana 59840-9307

Full name of sole or Third inventor: Norris, Daniel A.

Inventor's signature ______________________ Date 5/7/99

Residence: San Diego, California

Citizen of: United States of America

Post Office Address: 3145 Cowley Way, #130
San Diego, California 92117

Full name of sole or Fourth inventor: Sinko, Patrick J.

Inventor's signature ______________________ Date 5/10/99

Residence: Lebanon, New Jersey

Citizen of: United States of America

Post Office Address: 2 Country Place
Lebanon, New Jersey 08833

Full name of sole or Fifth inventor: Wehrli, John E.

Inventor's signature ____________________ Date 5/7/99

Residence: Mountain View, California

Citizen of: United States of America

Post Office Address: 1879 Springer Unit B
Mountain View, California 94040

CONFIDENTIAL

Attorney Docket No: NAVI-009/02US **PATENT**

Express Mail Label Number: EM 570 539 405 US
Date of Deposit: May 26, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

Date: 26 May 99 By: [signature] VLADIMIR SKLIBA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

09/318353 · 112201

In re application of George M. Grass, et al.

Serial No.:	Not yet assigned	Examiner:	Not yet assigned
Filed:	Herewith	Art Unit:	Not yet assigned

For: METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

Assistant Commissioner for Patents
BOX PATENT APPLICATION
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE AND EXCLUSION OF INVENTORS UNDER 37 CFR 1.36 AND 3.71

Sir:

The undersigned assignee of the entire interest in the application for Letters Patent identified above hereby revokes all prior appointments of attorneys and appoints

Nina M. Ashton	37,273	Marcella Lillis	36,583
Alexandra J. Baran	39,101	Tom M. Moran	26,314
James A. Bradburne	38,389	Richard L. Neeley	30,092
Aaron S. Brodsky	39,920	Craig P. Opperman	37,078
Shelley P. Eberle	31,411	Marya A. Postner	42,085
Richard M. Goldman	25,585	Gurjeev K. Sachdeva	37,434
Willis E. Higgins	23,025	William E. Winters	42,232
Peter R. Leal	24,226	Kevin J. Zimmer	36,977

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7R6_01!.DOC

all of the firm of Cooley Godward LLP, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith. This appointment shall be to the exclusion of the above-identified inventor(s) and any attorney(s) appointed by such inventor(s), in accordance with the provisions of 37 C.F.R. 1.36 and 3.71.

Assignee's rights are evidenced by an assignment

[X] a copy of which is enclosed herewith.

[] previously recorded on at reel , frame(s) .

Please direct all telephone calls and correspondence to:

Cooley Godward LLP
Attention: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Telephone: 650-843-5000
Facsimile: 650-857-0663

Assignee: Navicyte, Inc.

Signature: ______________________

Name: John E. Wehrli, Esq.

Title: Senior Director, Legal Affairs/ Corporate Secretary

Address: 9880 Campus Point Drive, San Diego, California 92121

Date: May 14, 1999

Attorney Docket No: NAVI-009/02US **PATENT**

Express Mail Label Number: EM 570 539 405 US
Date of Deposit: May 26, 1999

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

Date: 26 May 99 By: [signature]
VLADIMIR SKLIBA

10123456 "103101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of George M. Grass, et al.

Serial No.: Not yet assigned Examiner: Not yet assigned

Filed: May 26, 1999 Art Unit: Not yet assigned

For: METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

Assistant Commissioner for Patents
Washington, D.C. 20231

STATEMENT UNDER 37 CFR 3.73(b)
ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

1. The assignee(s) of the entire right, title and interest hereby seek(s) to take action in the PTO in this matter.

IDENTIFICATION OF ASSIGNEE

Name of Assignee: Navicyte, Incorporated

Type of Assignee: Corporation

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8J#S01!.DOC

PERSON AUTHORIZED TO SIGN

Name of Person Authorized to Sign: James A. Bradburne, Ph.D.

Title of Person Authorized to Sign: Agent of Record

[X] I, the person signing below, state that I am empowered to sign this statement on behalf of the assignee.

BASIS OF ASSIGNEE'S INTEREST

Ownership by the assignee is established as follows. A chain of title from the inventor(s) to the current assignee is shown below:

1. From: George M. Grass, Glen D. Leesman, Daniel A. Norris, Patrick J. Sinko and John E. Wehrli

   To: Navicyte, Incorporated

   Recordation Date: 12/22/98 Reel: 9673 Frame: 0774-0777

[ ] Copies of the documents in the chain of title are attached.

Cooley Godward LLP
Attn: Patent Group
Five Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306-2155
Tel: (650) 843-5000
Fax: (650) 857-0663

Respectfully submitted,
COOLEY GODWARD LLP

By: James A. Bradburne, Ph.D.
Reg. No. 38,389

JAB:pkp

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

GRASS et al.	Art Unit: 1631
Application No.: 09/320,069	Examiner: M. Moran
Filed: May 26, 1999	Attorney Dkt. No.: 109904-00027

For: METHOD FOR SCREENING AND PRODUCING COMPOUND LIBRARIES

REVOCATION OF POWER OF ATTORNEY AND NEW APPOINTMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

November 5, 2001

Sir:

Dr. Christian Kilger, the undersigned, certifies that Lion Bioscience AG is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 09/320,069, filed May 26, 1999, by virtue of an assignment from NaviCyte, Inc., a copy of which is attached hereto. The assignment to NaviCyte was recorded in the Patent and Trademark Office at Reel 9673, Frame 0774-0777 on December 22, 1998.

Further, Lion Bioscience AG, as assignee of the entire interest in and to the above-identified United States patent application hereby revokes all powers of attorney previously given and appoints Arent Fox Kintner Plotkin & Kahn, 1050 Connecticut Avenue, Suite 600, Washington, DC, 20036-5339, a firm composed of:

Charles M. Marmelstein, Reg. No. 25,895; **Robert B. Murray**, Reg. No. 22,980; **George E. Oram, Jr.**, Reg. No. 27,931; **Douglas H. Goldhush**, Reg. No. 33,125; **Richard J. Berman**, Reg. No. 39,107; **Murat Ozgu**, Reg. No. 44,275; **Robert K. Carpenter**, Reg. No. 34,794; **Gregory B. Kang**, Reg. No. 45,273; **Rustan Hill**, Reg. No. 37,351; **Kevin F. Turner**, Reg. No. 43,437; **Rhonda C. Barton**, Reg. No. P47,271 and **Hans J. Crosby,** Reg. No. 44,634, **Brian A. Tollefson**, Reg. No. 46,338, **Lynn D. Anderson**, Reg. No. 46,412, **David D. Dzara**, Reg. No. 47,543; **Laurence J. Edson**, Reg. No. 44,666; **Michael A. Steinberg**, Reg. No. 43,160; and **Lynn A. Bristol**, Reg. No. 48,898.

as principal attorneys to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith.

The undersigned has reviewed all of the appropriate documents and, to the best of the undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to sign this paper on behalf of the assignee.

By the provisions of 28 U.S.C. §1746, I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on: November 5, 2001
(date)

Name: Dr. Christian Kilger

Title: Director of IP and Licensing

Signature:

ATTACHED SHEET

U.S. Patent 5,183,760

U.S. Patent 5,591,636

U.S. Serial Number 09/320,069

U.S. Serial Number 09/320,270

U.S. Serial Number 09/320,545

U.S. Serial Number 60/224,106

U.S. Patent 5,599,688

U.S. Patent 6,146,883

U.S. Serial Number 09/320,372

U.S. Serial Number 09/320,371

U.S. Serial Number 09/320,544

ASSIGNMENT

WHEREAS, NaviCyte, Inc. (hereinafter ASSIGNOR) a company having its principal office and place of business at Sparks, Nevada, USA owns the inventions, and the patents and patent applications in various countries directed thereto, as set forth on the 2 page attachment hereto.

AND, WHEREAS, LION Bioscience AG (hereinafter ASSIGNEE), a company having its principal office and place of business at Heidelberg, Germany, is desirous of acquiring all interest therein.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the above said ASSIGNOR by these presents does sell, assign and transfer unto the said ASSIGNEE, its successors, assigns and legal representatives, the full and exclusive right, title and interest in and to the said inventions in the United States and other countries including the ful and extensive right, title and interest world-wide in and to the patents and patent applications on the attachment hereto.

NaviCyte, Inc.

By: ______________

Title:

Date: 6/6/01

Witness: ______________

6/6/01

APPENDICIES

Appendix 1: Abbreviation Key for Mass-Volume Model

Abbreviation
Kf sd = associated rate constant for stomach and duodenum
Ka dj = associated rate constant for duodenum and jejunum
Ka ji = associated rate constant for jejunum and ileum
Ka ie = associated rate constant for ileum and colon
Ka co = associated rate constant for colon and excretion
SD trans = transfer rate between stomach and duodenum
DJ trans = transfer rate between duodenum and jejunum
JL trans = transfer rate between jejunum and ileum
IC trans = transfer rate between ileum and colon
Waste = transfer rate between colon and excretion
pH s = pH stomach
pH s2 = pH duodenum
pH s3 = pH jejunum
pH s4 = pH ileum
pH s5 = pH colon
sol profile = solubility profile for stomach

sol profile 2 = solubility profile for duodenum
sol profile 3 = solubility profile for jejunum
sol profile 4 = solubility profile for ileum
sol profile 5 = solubility profile for colon
stom ka = associated rate constant for stomach compartments 1 and 2
duo ka = associated rate constant for duodenum compartments 1 and 2
Jej ka = associated rate constant for jejunum compartments 1 and 2
Il ka = associated rate constant for ileum compartments 1 and 2
Colon ka = associated rate constant for colon compartments 1 and 2
SA stom = surface area of stomach
SA duo = surface area of duodenum
SA jej = surface area of jejunum
SA il = surface area of ileum
SA colon = surface area of colon
Perm stom = permeability of stomach
Perm duo = permeability of duodenum
Perm jej = permeability of jejunum
Perm il = permeability of ileum
Perm colon = permeability of colon

Ka sd = associated rate construct for stomach fluid absorption
Ka du = associated rate construct for duodeunm fluid absorption
Ka je = associated rate construct for jejunm fluid absorption
Ka il = associated rate construct for ileunm fluid absorption
Ka co = associated rate construct for colon fluid absorption
Note: other abbreviations adhere to above descriptors and are self explanatory

Appendix 2: Equations, Parameters and Values For Mass-Volume Model

amt_plasma(t) = amt_plasma(t - dt) + (trans_21 + ka - elimination - trans_12) * dt
INIT amt_plasma = 0

INFLOWS:
trans_21 = k21*comp_2
ka = tot_abs_rate

OUTFLOWS:
elimination = amt_plasma*k_elim
trans_12 = k12*amt_plasma
blood_side_col(t) = blood_side_col(t - dt) + (colon_ka_5) * dt
INIT blood_side_col = 0

INFLOWS:
colon_ka_5 = IF Vol_colon*sol_profile_5 >=Colon THEN Colon*SA_colon*perm_colon*3600 ELSE Vol_colon*sol_profile_5*SA_colon*perm_colon*3600
blood_side_dou(t) = blood_side_dou(t - dt) + (duo_ka) * dt
INIT blood_side_dou = 0

INFLOWS:
duo_ka = IF Vol_duod*sol_profile_2 >= duodenum THEN duodenum*SA_duo*perm_duo*3600 ELSE Vol_duod*sol_profile_2*SA_duo*perm_duo*3600
blood_side_il(t) = blood_side_il(t - dt) + (Il_ka) * dt
INIT blood_side_il = 0

INFLOWS:
Il_ka = IF Vol_ileum*sol_profile_4 >=Ileum THEN Ileum*SA_Il*perm_Il*3600 ELSE Vol_ileum*sol_profile_4*SA_Il*perm_Il*3600
blood_side_jej(t) = blood_side_jej(t - dt) + (Jej_ka) * dt
INIT blood_side_jej = 0

INFLOWS:
Jej_ka = IF Vol_jej*sol_profile_3 >=Jejunum THEN Jejunum*SA_jej*perm_jej *3600 ELSE Vol_jej*sol_profile_3*SA_jej*perm_jej*3600
blood_side_sto(t) = blood_side_sto(t - dt) + (stom_ka) * dt
INIT blood_side_sto = 0

INFLOWS:
stom_ka = IF Vol_stom*sol_profile >= Stomach THEN Stomach*SA_stom*perm_stom*3600 ELSE Vol_stom*sol_profile*SA_stom*perm_stom*3600
Colon(t) = Colon(t - dt) + (IC_trans - Waste - colon_ka_5) * dt
INIT Colon = 0

INFLOWS:
IC_trans = ka_ic*Ileum

OUTFLOWS:
Waste = ka_col*Colon
colon_ka_5 = IF Vol_colon*sol_profile_5 >=Colon THEN Colon*SA_colon*perm_colon*3600 ELSE Vol_colon*sol_profile_5*SA_colon*perm_colon*3600
comp_2(t) = comp_2(t - dt) + (trans_12 - trans_21) * dt
INIT comp_2 = 0

INFLOWS:
trans_12 = k12*amt_plasma

OUTFLOWS:
trans_21 = k21*comp_2
duodenum(t) = duodenum(t - dt) + (SD_trans - duo_ka - DJ_trans) * dt
INIT duodenum = 0

INFLOWS:
SD_trans = if Stomach >0 then kf_sd*Stomach else 0

OUTFLOWS:
duo_ka = IF Vol_duod*sol_profile_2 >= duodenum THEN duodenum*SA_duo*perm_duo*3600 ELSE Vol_duod*sol_profile_2*SA_duo*perm_duo*3600
DJ_trans = ka_dj*duodenum
excretion(t) = excretion(t - dt) + (vol_cw) * dt
INIT excretion = 0

INFLOWS:
vol_cw = Vol_colon*ka_col
excretion_2(t) = excretion_2(t - dt) + (Waste) * dt
INIT excretion_2 = 0

INFLOWS:
Waste = ka_col*Colon
Ileum(t) = Ileum(t - dt) + (JL_trans - IC_trans - Il_ka) * dt
INIT Ileum = 0

INFLOWS:
JL_trans = ka_ji*Jejunum

OUTFLOWS:
IC_trans = ka_ic*Ileum
Il_ka = IF Vol_ileum*sol_profile_4 >=Ileum THEN Ileum*SA_Il*perm_Il*3600 ELSE Vol_ileum*sol_profile_4*SA_Il*perm_Il*3600
Jejunum(t) = Jejunum(t - dt) + (DJ_trans - JL_trans - Jej_ka) * dt

INIT Jejunum = 0

INFLOWS:
DJ_trans = ka_dj*duodenum

OUTFLOWS:
JL_trans = ka_ji*Jejunum
Jej_ka = IF Vol_jej*sol_profile_3 >=Jejunum THEN Jejunum*SA_jej*perm_jej *3600 ELSE Vol_jej*sol_profile_3*SA_jej*perm_jej*3600
serosal_col(t) = serosal_col(t - dt) + (Adsorp_col - col_secretion) * dt
INIT serosal_col = 0

INFLOWS:
Adsorp_col = PULSE(1.67,0,.1)+0*Vol_colon*ka_co

OUTFLOWS:
col_secretion = 0
serosal_dou(t) = serosal_dou(t - dt) + (Adsorp_Duo - duo_secretion) * dt
INIT serosal_dou = 0

INFLOWS:
Adsorp_Duo = PULSE(10.82,0,.1)+0*Vol_duod*ka_du

OUTFLOWS:
duo_secretion = PULSE(10.82,0,.1)
serosal_ill(t) = serosal_ill(t - dt) + (Adsorpt_ill - ile_secretion) * dt
INIT serosal_ill = 0

INFLOWS:
Adsorpt_ill = PULSE(8.83,0,.10)+0*Vol_ileum*ka_il

OUTFLOWS:
ile_secretion = PULSE(1.50,0,.1)
serosal_jej(t) = serosal_jej(t - dt) + (Adsorp_jej - jej_secretion) * dt
INIT serosal_jej = 0

INFLOWS:
Adsorp_jej = PULSE(15.76,0,.1)+0*Vol_jej*ka_je

OUTFLOWS:
jej_secretion = PULSE(2.67,0,.1)
serosal_sto(t) = serosal_sto(t - dt) + (Adsorp_Stom - Stom_Secretion) * dt
INIT serosal_sto = 0

INFLOWS:
Adsorp_Stom = 0*Vol_stom*ka_sd

```
OUTFLOWS:
Stom_Secretion = PULSE(16.67,0,.1)
Stomach(t) = Stomach(t - dt) + (- SD_trans - stom_ka) * dt
INIT Stomach = 1000

OUTFLOWS:
SD_trans = if Stomach >0 then kf_sd*Stomach else 0
stom_ka = IF Vol_stom*sol_profile >= Stomach THEN Stomach*SA_stom*perm_stom*3600
ELSE Vol_stom*sol_profile*SA_stom*perm_stom*3600
total_drug_absorbed(t) = total_drug_absorbed(t - dt) + (tot_abs_rate) * dt
INIT total_drug_absorbed = 0

INFLOWS:
tot_abs_rate = stom_ka+duo_ka+Jej_ka+Il_ka+colon_ka_5
Total_Elimination(t) = Total_Elimination(t - dt) + (elimination) * dt
INIT Total_Elimination = 0

INFLOWS:
elimination = amt_plasma*k_elim
Vol_colon(t) = Vol_colon(t - dt) + (vol_ij + col_secretion - vol_cw - Adsorp_col) * dt
INIT Vol_colon = 0

INFLOWS:
vol_ij = Vol_ileum*ka_ic
col_secretion = 0

OUTFLOWS:
vol_cw = Vol_colon*ka_col
Adsorp_col = PULSE(1.67,0,.1)+0*Vol_colon*ka_co
Vol_duod(t) = Vol_duod(t - dt) + (vol_sd + duo_secretion - voil_dj - Adsorp_Duo) * dt
INIT Vol_duod = 0

INFLOWS:
vol_sd = kf_sd*Vol_stom
duo_secretion = PULSE(10.82,0,.1)

OUTFLOWS:
voil_dj = Vol_duod*ka_dj
Adsorp_Duo = PULSE(10.82,0,.1)+0*Vol_duod*ka_du
Vol_ileum(t) = Vol_ileum(t - dt) + (vol_ji + ile_secretion - Adsorpt_ill - vol_ij) * dt
INIT Vol_ileum = 0

INFLOWS:
vol_ji = Vol_jej*ka_ji
ile_secretion = PULSE(1.50,0,.1)
```

```
OUTFLOWS:
Adsorpt_ill = PULSE(8.83,0,.10)+0*Vol_ileum*ka_il
vol_ij = Vol_ileum*ka_ic
Vol_jej(t) = Vol_jej(t - dt) + (voil_dj + jej_secretion - vol_ji - Adsorp_jej) * dt
INIT Vol_jej = 0

INFLOWS:
voil_dj = Vol_duod*ka_dj
jej_secretion = PULSE(2.67,0,.1)

OUTFLOWS:
vol_ji = Vol_jej*ka_ji
Adsorp_jej = PULSE(15.76,0,.1)+0*Vol_jej*ka_je
Vol_stom(t) = Vol_stom(t - dt) + (Stom_Secretion - vol_sd - Adsorp_Stom) * dt
INIT Vol_stom = PULSE(8.33,0,.1)

INFLOWS:
Stom_Secretion = PULSE(16.67,0,.1)

OUTFLOWS:
vol_sd = kf_sd*Vol_stom
Adsorp_Stom = 0*Vol_stom*ka_sd
conc_plasma = (amt_plasma/volume)*mg_to_ug
k12 = .839
k21 = .67
ka_co = 1
ka_col = 3
ka_dj = 3
ka_du = 1
ka_ic = 3
ka_il = 8.83
ka_je = 1
ka_ji = 3
ka_sd = 1
kf_sd = 2.8
k_elim = .161
mg_to_ug = 1000
perm_colon = 3.80e-6
perm_duo = 1.10e-6
perm_Il = 4.06e-6
perm_jej = 2.17e-6
perm_stom = 1.10e-6
ph_s = 1.5
ph_s_2 = 6.6
ph_s_3 = 6.6
```

```
ph_s_4 = 7.5
ph_s_5 = 6.6
SA_colon = 138
SA_duo = 125
SA_Il = 102
SA_jej = 182
SA_stom = 50
volume = 4*19200
sol_profile = GRAPH(ph_s)
(1.00, 63.0), (1.50, 25.0), (2.00, 10.0), (2.50, 5.00), (3.00, 4.00), (3.50, 3.80), (4.00, 3.65), (4.50, 3.50), (5.00, 3.65), (5.50, 3.65), (6.00, 3.65), (6.50, 3.65), (7.00, 3.65), (7.50, 3.65), (8.00, 3.65), (8.50, 4.00), (9.00, 5.00), (9.50, 12.0), (10.0, 23.5)
sol_profile_2 = GRAPH(ph_s_2)
(1.00, 63.0), (1.50, 25.0), (2.00, 10.0), (2.50, 5.00), (3.00, 4.00), (3.50, 3.80), (4.00, 3.65), (4.50, 3.50), (5.00, 3.65), (5.50, 3.65), (6.00, 3.65), (6.50, 3.65), (7.00, 3.65), (7.50, 3.65), (8.00, 3.65), (8.50, 4.00), (9.00, 5.00), (9.50, 12.0), (10.0, 23.5)
sol_profile_3 = GRAPH(ph_s_3)
(1.00, 63.0), (1.50, 25.0), (2.00, 10.0), (2.50, 5.00), (3.00, 4.00), (3.50, 3.80), (4.00, 3.65), (4.50, 3.50), (5.00, 3.65), (5.50, 3.65), (6.00, 3.65), (6.50, 3.65), (7.00, 3.65), (7.50, 3.65), (8.00, 3.65), (8.50, 4.00), (9.00, 5.00), (9.50, 12.0), (10.0, 23.5)
sol_profile_4 = GRAPH(ph_s_4)
(1.00, 63.0), (1.50, 25.0), (2.00, 10.0), (2.50, 5.00), (3.00, 4.00), (3.50, 3.80), (4.00, 3.65), (4.50, 3.50), (5.00, 3.65), (5.50, 3.65), (6.00, 3.65), (6.50, 3.65), (7.00, 3.65), (7.50, 3.65), (8.00, 3.65), (8.50, 4.00), (9.00, 5.00), (9.50, 12.0), (10.0, 23.5)
sol_profile_5 = GRAPH(ph_s_5)
(1.00, 63.0), (1.50, 25.0), (2.00, 10.0), (2.50, 5.00), (3.00, 4.00), (3.50, 3.80), (4.00, 3.65), (4.50, 3.50), (5.00, 3.65), (5.50, 3.65), (6.00, 3.65), (6.50, 3.65), (7.00, 3.65), (7.50, 3.65), (8.00, 3.65), (8.50, 4.00), (9.00, 5.00), (9.50, 12.0), (10.0, 23.5)
```

Appendix 3: Abbreviation Key For GI Model

The legend/key has been divided into sub-sections corresponding to the sub-sections of the model diagram.

Numbered suffixes (1, 2, 3, 4, 5, 6) have been assigned to distinguish between intestinal regions (stomach, duodenum, jejunum, ileum, colon, and waste, respectively).

1 – stomach
2 – duodenum
3 – jejunum
4 – ileum
5 – colon
6 – waste

For example, VOL 1 is the volume in the stomach, MASS 3 is the insoluble mass in the jejunum. In the equations, COMP 1 indicates the stomach, COMP 2 the duodenum, COMP 3, the jejunum, etc.

Ghosts are listed under the sub-section containing the original reservoir, flow regulator, or converter.

Abbreviations listed in italics are regionally dependent and set up as arrays to allow independent values for each intestinal region.

In general, ADJ as a prefix indicates a calculated parameter value (ADJ = adjusted), while ADJ as a suffix indicates an adjustment parameter (ADJ = adjustment).

Intestinal model

Reservoirs/Compartments

VOL ABS	Fluid volume absorbed
VOL	Fluid volume
C REL	Mass of drug contained with a formulation or controlled release device
MASS	Insoluble mass of drug (not contained within the formulation or controlled release device)
SOL	Soluble mass of drug
ABSORPTION	Mass of drug absorbed

Flow regulators

REABS	Rate of water absorption
VOL OUT	Fluid volume transit rate
CR OUT	Formulation or controlled release device transit rate
CR INPUT	Drug release rate from formulation or controlled release device
MASS OUT	Insoluble drug mass transit rate
DISS PRECIP	Dissolution rate
SOL OUT	Soluble drug mass transit rate
FLUX	Absorption rate

ADJ PARMS (Adjustment Parameters)

VOL ADJ	Fluid volume absorption adjustment parameter
DISS ADJ	Dissolution rate adjustment parameter
TRANSIT ADJ	Transit time adjustment parameter
SA ADJ	Surface area adjustment parameter
FLUX ADJ	Passive Absorption adjustment parameter
EFFLUX ADJ	Efflux or secretion adjustment parameter
CARRIER ADJ	Active absorption adjustment parameter

PARMS (Parameters)

VOL PARM	Fluid volume absorption rate constant
SURFACE AREA	Surface area available for absorption
DOSE	The administered dose of drug
INIT VOLUME	The administered volume of water or fluid
TIME IN HOURS	A clock
pH	The physiological pH value
PARACELLULAR	A user controlled switch used to adjust absorption based on absorption mechanism

TRANSIT TIME

TRANSFERS	GI transit rate constant
CUMU TT	Cumulative transit time
ADJ TRANSIT TIME	Adjusted GI transit time incorporating adjustment parameter and user input
USER TT INPUT	User controlled adjustments to the GI transit time

OUTPUT CALCULATIONS

ABSORBED TOTAL	Total mass of drug absorbed (sum of ABSORPTION 1...5)

FDp%	Fraction or the dose absorbed into portal vein x 100
FLUX TOTAL	Total absorption rate (sum of FLUX 1...5)
CUM DISS	Cumulative drug mass dissolved
CR Release	Cumulative drug mass released from formulation
CUM DISS RATE	Sum of DISS PRECIP 1...5
CR cumrate	Summ of CR INPUT 1...5

PERMEABILITY CALCULATION

ADJ PERM	Adjusted permeability ncorporating all transport mechanisms and relevant adjustment parameters
ACT PE	Active or carrier-mediated absorptive permeability
Km	Constant from the Michaelis-Mentin type permeability equation for active transport
REGIONAL	Passive permeability after regional correlation calculation (same as PASS PE if regional correlation is not used)
PASS PE	Passive permeability entered by user
RC	A logical function used in determining the regional correlation
RCSUM	A logical function used in determining the regional correlation

SOLUBILITY CALCULATION

USER pH	User supplied pH value for which a solubility value is available
USER SOLUB	User supplied solubility value corresponding to the USER pH value
ADJ SOLUB	Solubility calculated (if necessary) at the appropriate pH value using the entered USER pH and USER SOLUB values

CONTROLLED RELEASE CALCULATION

CR RATE	The instantaneous release rate from the formulation
CR DOSE	The total dose contained with the formulation
CR AT TIME	The cumulative drug mass release profile
CR AT LAST	The cumulative drug mass release profile

Note: CR AT TIME holds the value at the current time value (t), CR AT LAST holds the value at the immediately preceeding time value (t-1)

CONC CALCULATION

CONCENTRATIONS	The dissolved drug concentration

DISSOLUTION CALCULATION

PRECIP	Precipitation rate constant
DISSOL	Dissolution rate constant
ADJ DISS PRECIP	Adjusted rate constant incorporating PRECIP, DISSOL and calculated concentration

Appendix 4: Equations, Parameters and Values For GI Model

ADJ PARMS

- CARRIER_ADJ[COMPS] = 0
- DISS_ADJ[COMP_1] = 1
- DISS_ADJ[COMP_2] = 1
- DISS_ADJ[COMP_3] = 1
- DISS_ADJ[COMP_4] = 1
- DISS_ADJ[COMP_5] = 1
- EFFLUX_ADJ[COMPS] = 1
- FLUX_ADJ[COMP_1] = 1
- FLUX_ADJ[COMP_2] = 10
- FLUX_ADJ[COMP_3] = 8
- FLUX_ADJ[COMP_4] = 2
- FLUX_ADJ[COMP_5] = 1
- SA_ADJ[COMP_1] = 1
- SA_ADJ[COMP_2] = 1
- SA_ADJ[COMP_3] = 1
- SA_ADJ[COMP_4] = 1
- SA_ADJ[COMP_5] = 1
- TRANSIT_ADJ[COMP_1] = 1
- TRANSIT_ADJ[COMP_2] = 1
- TRANSIT_ADJ[COMP_3] = 1
- TRANSIT_ADJ[COMP_4] = 1
- TRANSIT_ADJ[COMP_5] = 1
- VOL_ADJ[COMP_1] = 1
- VOL_ADJ[COMP_2] = 1
- VOL_ADJ[COMP_3] = 1
- VOL_ADJ[COMP_4] = 1
- VOL_ADJ[COMP_5] = 1

CONC CALCULATION

- CONCENTRATIONS[COMP_1] = if VOL_1=0.0 then 0 else if ADJ_SOLUB[COMP_1]<SOL_1/VOL_1 then ADJ_SOLUB[COMP_1] else SOL_1/VOL_1 + 0*(SOL_2+SOL_5+SOL_3+SOL_4+VOL_3+VOL_2+VOL_4+VOL_5)
- CONCENTRATIONS[COMP_2] = if VOL_2 = 0.0 then 0 else if (VOL_2<1e-6 AND SOL_2<1e-7) then 0 else if ADJ_SOLUB[COMP_2]<SOL_2/VOL_2 then ADJ_SOLUB[COMP_2] else SOL_2/VOL_2 +0*(SOL_1+SOL_5+SOL_3+SOL_4+VOL_3+VOL_1+VOL_5+VOL_4)
- CONCENTRATIONS[COMP_3] = if VOL_3 = 0.0 then 0 else if (VOL_3<1e-6 AND SOL_3<1e-7) then 0 else if ADJ_SOLUB[COMP_3]<SOL_3/VOL_3 then ADJ_SOLUB[COMP_3] else SOL_3/VOL_3 +0*(SOL_1+SOL_2+SOL_4+SOL_5+VOL_5+VOL_4+VOL_1+VOL_2)
- CONCENTRATIONS[COMP_4] = if VOL_4 = 0.0 then 0 else if (VOL_4<1e-6 AND SOL_4<1e-7) then 0 else if ADJ_SOLUB[COMP_4]<SOL_4/VOL_4 then ADJ_SOLUB[COMP_4] else SOL_4/VOL_4 +0*(SOL_1+SOL_2+SOL_3+SOL_5+VOL_1+VOL_2+VOL_3+VOL_5)

CONCENTRATIONS[COMP_5] = if VOL_5 = 0.0 then 0 else if (VOL_5<1e-6 AND SOL_5<1e-7) then 0 else if ADJ_SOLUB[COMP_5]<SOL_5/VOL_5 then ADJ_SOLUB[COMP_5] else SOL_5/VOL_5
+0*(SOL_1+SOL_4+SOL_3+SOL_2+VOL_3+VOL_1+VOL_2+VOL_4)

CONTROL RELEASE CALCULATION

CR_DOSE = 0

CR_RATE = (CR_AT_TIME-CR_AT_LAST)*20*(CR_DOSE/100)

CR_AT_LAST = GRAPH(TIME-DT)
(0.00, 0.00), (0.25, 17.7), (0.5, 31.5), (0.75, 42.2), (1.00, 50.6), (1.25, 57.1), (1.50, 62.1), (1.75, 66.1), (2.00, 69.2), (2.25, 71.6), (2.50, 73.4), (2.75, 74.9), (3.00, 76.0), (3.25, 76.9), (3.50, 77.6), (3.75, 78.1), (4.00, 78.5), (4.25, 78.9), (4.50, 79.1), (4.75, 79.3), (5.00, 79.5), (5.25, 79.6), (5.50, 79.7), (5.75, 79.7), (6.00, 79.8), (6.25, 79.8), (6.50, 79.9), (6.75, 79.9), (7.00, 79.9), (7.25, 79.9), (7.50, 80.0), (7.75, 80.0), (8.00, 80.0), (8.25, 80.0), (8.50, 80.0), (8.75, 80.0), (9.00, 80.0), (9.25, 80.0), (9.50, 80.0), (9.75, 80.0), (10.0, 80.0), (10.3, 80.0), (10.5, 80.0), (10.8, 80.0), (11.0, 80.0), (11.3, 80.0), (11.5, 80.0), (11.8, 80.0), (12.0, 80.0), (12.3, 80.0), (12.5, 80.0), (12.8, 80.0), (13.0, 80.0)...

CR_AT_TIME = GRAPH(TIME)
(0.00, 0.00), (0.25, 17.7), (0.5, 31.5), (0.75, 42.2), (1.00, 50.6), (1.25, 57.1), (1.50, 62.1), (1.75, 66.1), (2.00, 69.2), (2.25, 71.6), (2.50, 73.4), (2.75, 74.9), (3.00, 76.0), (3.25, 76.9), (3.50, 77.6), (3.75, 78.1), (4.00, 78.5), (4.25, 78.9), (4.50, 79.1), (4.75, 79.3), (5.00, 79.5), (5.25, 79.6), (5.50, 79.7), (5.75, 79.7), (6.00, 79.8), (6.25, 79.8), (6.50, 79.9), (6.75, 79.9), (7.00, 79.9), (7.25, 79.9), (7.50, 80.0), (7.75, 80.0), (8.00, 80.0), (8.25, 80.0), (8.50, 80.0), (8.75, 80.0), (9.00, 80.0), (9.25, 80.0), (9.50, 80.0), (9.75, 80.0), (10.0, 80.0), (10.3, 80.0), (10.5, 80.0), (10.8, 80.0), (11.0, 80.0), (11.3, 80.0), (11.5, 80.0), (11.8, 80.0), (12.0, 80.0), (12.3, 80.0), (12.5, 80.0), (12.8, 80.0), (13.0, 80.0)...

DISSOLUTION CALCULATION

ADJ_DISS_PRECIP[COMP_1] = if VOL_1=0 then 0 else if (SOL_1/VOL_1<ADJ_SOLUB[COMP_1]) then (DISSOL[COMP_1]*DISS_ADJ[COMP_1]*MASS_1*(ADJ_SOLUB[COMP_1]-SOL_1/VOL_1)) else ((SOL_1/VOL_1)-ADJ_SOLUB[COMP_1])*PRECIP[COMP_1]+
0*(MASS_1+MASS_2+MASS_3+MASS_4+MASS_5+SOL_1+SOL_2+SOL_3+SOL_4+SOL_5+VOL_1+VOL_2+VOL_3+VOL_4+VOL_5)

ADJ_DISS_PRECIP[COMP_2] = if VOL_2=0 then 0 else if (SOL_2/VOL_2<ADJ_SOLUB[COMP_2]) then (DISSOL[COMP_2]*DISS_ADJ[COMP_2]*MASS_2*(ADJ_SOLUB[COMP_2]-SOL_2/VOL_2)) else ((SOL_2/VOL_2)-ADJ_SOLUB[COMP_2])*PRECIP[COMP_2]
+0*(MASS_1+MASS_2+MASS_3+MASS_4+MASS_5+SOL_1+SOL_2+SOL_3+SOL_4+SOL_5+VOL_1+VOL_2+VOL_3+VOL_4+VOL_5)

ADJ_DISS_PRECIP[COMP_3] = if VOL_3=0 then 0 else if (SOL_3/VOL_3<ADJ_SOLUB[COMP_3]) then (DISSOL[COMP_3]*DISS_ADJ[COMP_3]*MASS_3*(ADJ_SOLUB[COMP_3]-SOL_3/VOL_3)) else ((SOL_3/VOL_3)-ADJ_SOLUB[COMP_3])*PRECIP[COMP_3]
+0*(MASS_1+MASS_2+MASS_3+MASS_4+MASS_5+SOL_1+SOL_2+SOL_3+SOL_4+SOL_5+VOL_1+VOL_2+VOL_3+VOL_4+VOL_5)

```
ADJ_DISS_PRECIP[COMP_4] = if VOL_4=0 then 0 else if
(SOL_4/VOL_4<ADJ_SOLUB[COMP_4]) then
(DISSOL[COMP_4]*DISS_ADJ[COMP_4]*MASS_4*(ADJ_SOLUB[COMP_4]-SOL_4/VOL_4)) else
((SOL_4/VOL_4)-ADJ_SOLUB[COMP_4])*PRECIP[COMP_4]
+0*(MASS_1+MASS_2+MASS_3+MASS_4+MASS_5+SOL_1+SOL_2+SOL_3+SOL_4+SOL_5+V
OL_1+VOL_2+VOL_3+VOL_4+VOL_5)
ADJ_DISS_PRECIP[COMP_5] = if VOL_5=0 then 0 else if
(SOL_5/VOL_5<ADJ_SOLUB[COMP_5]) then
(DISSOL[COMP_5]*DISS_ADJ[COMP_5]*MASS_5*(ADJ_SOLUB[COMP_5]-SOL_5/VOL_5)) else
((SOL_5/VOL_5)-ADJ_SOLUB[COMP_5])*PRECIP[COMP_5]
+0*(MASS_1+MASS_2+MASS_3+MASS_4+MASS_5+SOL_1+SOL_2+SOL_3+SOL_4+SOL_5+V
OL_1+VOL_2+VOL_3+VOL_4+VOL_5)
DISSOL[COMP_1] = 1
DISSOL[COMP_2] = 1
DISSOL[COMP_3] = 1
DISSOL[COMP_4] = 1
DISSOL[COMP_5] = 1
PRECIP[COMP_1] = 10
PRECIP[COMP_2] = 10
PRECIP[COMP_3] = 10
PRECIP[COMP_4] = 10
PRECIP[COMP_5] = 10
INPUTS
INTESTINAL MODEL
ABSORPTION_1(t) = ABSORPTION_1(t - dt) + (FLUX_1) * dt
INIT ABSORPTION_1 = 0
 INFLOWS:
   FLUX_1 =
   CONCENTRATIONS[COMP_1]*ADJ_PERM[COMP_1]*SURFACE_AREA[COMP_1]

ABSORPTION_2(t) = ABSORPTION_2(t - dt) + (FLUX_2) * dt
INIT ABSORPTION_2 = 0
 INFLOWS:
   FLUX_2 =
   CONCENTRATIONS[COMP_2]*ADJ_PERM[COMP_2]*SURFACE_AREA[COMP_2]

ABSORPTION_3(t) = ABSORPTION_3(t - dt) + (FLUX_3) * dt
INIT ABSORPTION_3 = 0
 INFLOWS:
   FLUX_3 =
   CONCENTRATIONS[COMP_3]*ADJ_PERM[COMP_3]*SURFACE_AREA[COMP_3]

ABSORPTION_4(t) = ABSORPTION_4(t - dt) + (FLUX_4) * dt
INIT ABSORPTION_4 = 0
 INFLOWS:
```

```
FLUX_4 =
CONCENTRATIONS[COMP_4]*ADJ_PERM[COMP_4]*SURFACE_AREA[COMP_4]
ABSORPTION_5(t) = ABSORPTION_5(t - dt) + (FLUX_5) * dt
INIT ABSORPTION_5 = 0
INFLOWS:
FLUX_5 = if time<32 then
CONCENTRATIONS[COMP_5]*ADJ_PERM[COMP_5]*SURFACE_AREA[COMP_5]*(32-ti
me)/48*(VOL_5/17.2) else 0
C_REL_1(t) = C_REL_1(t - dt) + (- CR_OUT_1 - CR_INPUT_1) * dt
INIT C_REL_1 = CR_DOSE
OUTFLOWS:
CR_OUT_1 = IF TIME >= CUMU_TT[COMP_1] THEN C_REL_1*10000 ELSE 0
CR_INPUT_1 = if TIME>CUMU_TT[COMP_1] then 0 else CR_RATE
C_REL_2(t) = C_REL_2(t - dt) + (CR_OUT_1 - CR_OUT_2 - CR_INPUT_2) * dt
INIT C_REL_2 = 0
INFLOWS:
CR_OUT_1 = IF TIME >= CUMU_TT[COMP_1] THEN C_REL_1*10000 ELSE 0
OUTFLOWS:
CR_OUT_2 = IF TIME >= CUMU_TT[COMP_2] THEN C_REL_2*10000 ELSE 0
CR_INPUT_2 = if TIME>CUMU_TT[COMP_2] then 0 else CR_RATE
C_REL_3(t) = C_REL_3(t - dt) + (CR_OUT_2 - CR_OUT_3 - CR_INPUT_3) * dt
INIT C_REL_3 = 0
INFLOWS:
CR_OUT_2 = IF TIME >= CUMU_TT[COMP_2] THEN C_REL_2*10000 ELSE 0
OUTFLOWS:
CR_OUT_3 = IF TIME >= CUMU_TT[COMP_3] THEN C_REL_3*10000 ELSE 0
CR_INPUT_3 = if TIME > CUMU_TT[COMP_3] then 0 else CR_RATE
C_REL_4(t) = C_REL_4(t - dt) + (CR_OUT_3 - CR_OUT_4 - CR_INPUT_4) * dt
INIT C_REL_4 = 0
INFLOWS:
CR_OUT_3 = IF TIME >= CUMU_TT[COMP_3] THEN C_REL_3*10000 ELSE 0
OUTFLOWS:
CR_OUT_4 = IF TIME >= CUMU_TT[COMP_4] THEN C_REL_4*10000 ELSE 0
CR_INPUT_4 = if TIME>CUMU_TT[COMP_4] then 0 else CR_RATE
C_REL_5(t) = C_REL_5(t - dt) + (CR_OUT_4 - CR_OUT_5 - CR_INPUT_5) * dt
INIT C_REL_5 = 0
INFLOWS:
CR_OUT_4 = IF TIME >= CUMU_TT[COMP_4] THEN C_REL_4*10000 ELSE 0
OUTFLOWS:
CR_OUT_5 = IF TIME >= CUMU_TT[COMP_5] THEN C_REL_5*10000 ELSE 0
CR_INPUT_5 = if TIME>CUMU_TT[COMP_5] then 0 else CR_RATE
C_REL_6(t) = C_REL_6(t - dt) + (CR_OUT_5) * dt
INIT C_REL_6 = 0
INFLOWS:
CR_OUT_5 = IF TIME >= CUMU_TT[COMP_5] THEN C_REL_5*10000 ELSE 0
```

```
MASS_1(t) = MASS_1(t - dt) + (CR_INPUT_1 - MASS_OUT_1 - DISS_PRECIP_1) * dt
INIT MASS_1 = DOSE
 INFLOWS:
   CR_INPUT_1 = if TIME>CUMU_TT[COMP_1] then 0 else CR_RATE
 OUTFLOWS:
   MASS_OUT_1 = MASS_1*TRANSFERS[COMP_1]
   DISS_PRECIP_1 = ADJ_DISS_PRECIP[COMP_1]
MASS_2(t) = MASS_2(t - dt) + (MASS_OUT_1 + CR_INPUT_2 - MASS_OUT_2 -
DISS_PRECIP_2) * dt
INIT MASS_2 = 0
 INFLOWS:
   MASS_OUT_1 = MASS_1*TRANSFERS[COMP_1]
   CR_INPUT_2 = if TIME>CUMU_TT[COMP_2] then 0 else CR_RATE
 OUTFLOWS:
   MASS_OUT_2 = MASS_2*TRANSFERS[COMP_2]
   DISS_PRECIP_2 = ADJ_DISS_PRECIP[COMP_2]
MASS_3(t) = MASS_3(t - dt) + (CR_INPUT_3 + MASS_OUT_2 - MASS_OUT_3 -
DISS_PRECIP_3) * dt
INIT MASS_3 = 0
 INFLOWS:
   CR_INPUT_3 = if TIME > CUMU_TT[COMP_3] then 0 else CR_RATE
   MASS_OUT_2 = MASS_2*TRANSFERS[COMP_2]
 OUTFLOWS:
   MASS_OUT_3 = MASS_3*TRANSFERS[COMP_3]
   DISS_PRECIP_3 = ADJ_DISS_PRECIP[COMP_3]
MASS_4(t) = MASS_4(t - dt) + (CR_INPUT_4 + MASS_OUT_3 - MASS_OUT_4 -
DISS_PRECIP_4) * dt
INIT MASS_4 = 0
 INFLOWS:
   CR_INPUT_4 = if TIME>CUMU_TT[COMP_4] then 0 else CR_RATE
   MASS_OUT_3 = MASS_3*TRANSFERS[COMP_3]
 OUTFLOWS:
   MASS_OUT_4 = MASS_4*TRANSFERS[COMP_4]
   DISS_PRECIP_4 = ADJ_DISS_PRECIP[COMP_4]
MASS_5(t) = MASS_5(t - dt) + (CR_INPUT_5 + MASS_OUT_4 - MASS_OUT_5 -
DISS_PRECIP_5) * dt
INIT MASS_5 = 0
 INFLOWS:
   CR_INPUT_5 = if TIME>CUMU_TT[COMP_5] then 0 else CR_RATE
   MASS_OUT_4 = MASS_4*TRANSFERS[COMP_4]
 OUTFLOWS:
   MASS_OUT_5 = if time>4 then MASS_5*TRANSFERS[COMP_5] else 0
   DISS_PRECIP_5 = ADJ_DISS_PRECIP[COMP_5]
MASS_6(t) = MASS_6(t - dt) + (MASS_OUT_5) * dt
INIT MASS_6 = 0
 INFLOWS:
```

```
MASS_OUT_5 = if tim >4 th n MASS_5*TRANSFERS[COMP_5] else 0
SOL_1(t) = SOL_1(t - dt) + (DISS_PRECIP_1 - SOL_OUT_1 - FLUX_1) * dt
INIT SOL_1 = 0
INFLOWS:
  DISS_PRECIP_1 = ADJ_DISS_PRECIP[COMP_1]
OUTFLOWS:
  SOL_OUT_1 = SOL_1*TRANSFERS[COMP_1]
  FLUX_1 =
  CONCENTRATIONS[COMP_1]*ADJ_PERM[COMP_1]*SURFACE_AREA[COMP_1]

SOL_2(t) = SOL_2(t - dt) + (SOL_OUT_1 + DISS_PRECIP_2 - SOL_OUT_2 - FLUX_2) * dt
INIT SOL_2 = 0

INFLOWS:
  SOL_OUT_1 = SOL_1*TRANSFERS[COMP_1]
  DISS_PRECIP_2 = ADJ_DISS_PRECIP[COMP_2]
OUTFLOWS:
  SOL_OUT_2 = SOL_2*TRANSFERS[COMP_2]
  FLUX_2 =
  CONCENTRATIONS[COMP_2]*ADJ_PERM[COMP_2]*SURFACE_AREA[COMP_2]

SOL_3(t) = SOL_3(t - dt) + (DISS_PRECIP_3 + SOL_OUT_2 - SOL_OUT_3 - FLUX_3) * dt
INIT SOL_3 = 0

INFLOWS:
  DISS_PRECIP_3 = ADJ_DISS_PRECIP[COMP_3]
  SOL_OUT_2 = SOL_2*TRANSFERS[COMP_2]
OUTFLOWS:
  SOL_OUT_3 = SOL_3*TRANSFERS[COMP_3]
  FLUX_3 =
  CONCENTRATIONS[COMP_3]*ADJ_PERM[COMP_3]*SURFACE_AREA[COMP_3]

SOL_4(t) = SOL_4(t - dt) + (DISS_PRECIP_4 + SOL_OUT_3 - SOL_OUT_4 - FLUX_4) * dt
INIT SOL_4 = 0

INFLOWS:
  DISS_PRECIP_4 = ADJ_DISS_PRECIP[COMP_4]
  SOL_OUT_3 = SOL_3*TRANSFERS[COMP_3]
OUTFLOWS:
  SOL_OUT_4 = SOL_4*TRANSFERS[COMP_4]
  FLUX_4 =
  CONCENTRATIONS[COMP_4]*ADJ_PERM[COMP_4]*SURFACE_AREA[COMP_4]

SOL_5(t) = SOL_5(t - dt) + (DISS_PRECIP_5 + SOL_OUT_4 - SOL_OUT_5 - FLUX_5) * dt
INIT SOL_5 = 0

INFLOWS:
```

```
DISS_PRECIP_5 = ADJ_DISS_PRECIP[COMP_5]
SOL_OUT_4 = SOL_4*TRANSFERS[COMP_4]
OUTFLOWS:
SOL_OUT_5 = if time>4 then SOL_5*TRANSFERS[COMP_5] else 0
FLUX_5 = if time<32 then
CONCENTRATIONS[COMP_5]*ADJ_PERM[COMP_5]*SURFACE_AREA[COMP_5]*(32-ti
me)/48*(VOL_5/17.2) else 0
SOL_6(t) = SOL_6(t - dt) + (SOL_OUT_5) * dt
INIT SOL_6 = 0
INFLOWS:
SOL_OUT_5 = if time>4 then SOL_5*TRANSFERS[COMP_5] else 0
VOL_1(t) = VOL_1(t - dt) + (- REABS_1 - VOL_OUT_1) * dt
INIT VOL_1 = INIT_VOLUME
OUTFLOWS:
REABS_1 = VOL_1*VOL_PARM[COMP_1]
VOL_OUT_1 = VOL_1*TRANSFERS[COMP_1]
VOL_2(t) = VOL_2(t - dt) + (VOL_OUT_1 - VOL_OUT_2 - REABS_2) * dt
INIT VOL_2 = 0
INFLOWS:
VOL_OUT_1 = VOL_1*TRANSFERS[COMP_1]
OUTFLOWS:
VOL_OUT_2 = VOL_2*TRANSFERS[COMP_2]
REABS_2 = VOL_2*VOL_PARM[COMP_2]
VOL_3(t) = VOL_3(t - dt) + (VOL_OUT_2 - VOL_OUT_3 - REABS_3) * dt
INIT VOL_3 = 0
INFLOWS:
VOL_OUT_2 = VOL_2*TRANSFERS[COMP_2]
OUTFLOWS:
VOL_OUT_3 = VOL_3*TRANSFERS[COMP_3]
REABS_3 = VOL_3*VOL_PARM[COMP_3]
VOL_4(t) = VOL_4(t - dt) + (VOL_OUT_3 - VOL_OUT_4 - REABS_4) * dt
INIT VOL_4 = 0
INFLOWS:
VOL_OUT_3 = VOL_3*TRANSFERS[COMP_3]
OUTFLOWS:
VOL_OUT_4 = VOL_4*TRANSFERS[COMP_4]
REABS_4 = VOL_4*VOL_PARM[COMP_4]
VOL_5(t) = VOL_5(t - dt) + (VOL_OUT_4 - VOL_OUT_5 - REABS_5) * dt
INIT VOL_5 = 0
INFLOWS:
VOL_OUT_4 = VOL_4*TRANSFERS[COMP_4]
OUTFLOWS:
VOL_OUT_5 = VOL_5*TRANSFERS[COMP_5]
REABS_5 = VOL_5*VOL_PARM[COMP_5]
VOL_6(t) = VOL_6(t - dt) + (VOL_OUT_5) * dt
INIT VOL_6 = 0
```

```
    INFLOWS:
        VOL_OUT_5 = VOL_5*TRANSFERS[COMP_5]
VOL_ABS_1(t) = VOL_ABS_1(t - dt) + (REABS_1) * dt
INIT VOL_ABS_1 = 0
    INFLOWS:
        REABS_1 = VOL_1*VOL_PARM[COMP_1]
VOL_ABS_2(t) = VOL_ABS_2(t - dt) + (REABS_2) * dt
INIT VOL_ABS_2 = 0
    INFLOWS:
        REABS_2 = VOL_2*VOL_PARM[COMP_2]
VOL_ABS_3(t) = VOL_ABS_3(t - dt) + (REABS_3) * dt
INIT VOL_ABS_3 = 0
    INFLOWS:
        REABS_3 = VOL_3*VOL_PARM[COMP_3]
VOL_ABS_4(t) = VOL_ABS_4(t - dt) + (REABS_4) * dt
INIT VOL_ABS_4 = 0
    INFLOWS:
        REABS_4 = VOL_4*VOL_PARM[COMP_4]
VOL_ABS_5(t) = VOL_ABS_5(t - dt) + (REABS_5) * dt
INIT VOL_ABS_5 = 0
    INFLOWS:
        REABS_5 = VOL_5*VOL_PARM[COMP_5]
MULTI DOSE CALCULATION
OUTPUT CALCULATIONS
CR_Release(t) = CR_Release(t - dt) + (CR_cumrate) * dt
INIT CR_Release = 0
    INFLOWS:
        CR_cumrate = CR_INPUT_1+CR_INPUT_2+CR_INPUT_3+CR_INPUT_4+CR_INPUT_5
CUM_DISS(t) = CUM_DISS(t - dt) + (CUMM_DISS_RATE) * dt
INIT CUM_DISS = 0
    INFLOWS:
        CUMM_DISS_RATE =
        DISS_PRECIP_1+DISS_PRECIP_2+DISS_PRECIP_3+DISS_PRECIP_4+DISS_PRECIP
        5
ABSORBED_TOTAL = ABSORPTION_2+ABSORPTION_3+ABSORPTION_4+ABSORPTION_5
FDp% = ABSORBED_TOTAL/DOSE*100
FLUX_TOTAL = FLUX_2+FLUX_3+FLUX_4+FLUX_5
PARMS
DOSE = 1000
INIT_VOLUME = 100
PARACELLULAR = 1
pH[COMP_1] = 1.5
pH[COMP_2] = 5
pH[COMP_3] = 6.5
```

pH[COMP_4] = 7
pH[COMP_5] = 6.5
SURFACE_AREA[COMP_1] = if PARACELLULAR =0 then 50*SA_ADJ[COMP_1] else 50*SA_ADJ[COMP_1]
SURFACE_AREA[COMP_2] = if PARACELLULAR=0 then 150*SA_ADJ[COMP_2] else 7.5*SA_ADJ[COMP_2]
SURFACE_AREA[COMP_3] = if PARACELLULAR=0 then 1000*SA_ADJ[COMP_3] else 50*SA_ADJ[COMP_3]
SURFACE_AREA[COMP_4] = if PARACELLULAR=0 then 1000*SA_ADJ[COMP_4] else 50*SA_ADJ[COMP_4]
SURFACE_AREA[COMP_5] = if PARACELLULAR=0 then 850*SA_ADJ[COMP_5] else 42.5*SA_ADJ[COMP_5]
TIME_IN_HOURS = TIME
VOL_PARM[COMP_1] = 0*VOL_ADJ[COMP_1]
VOL_PARM[COMP_2] = 0*VOL_ADJ[COMP_2]
VOL_PARM[COMP_3] = 1.75*VOL_ADJ[COMP_3]
VOL_PARM[COMP_4] = 1.75*VOL_ADJ[COMP_4]
VOL_PARM[COMP_5] = 0.10*VOL_ADJ[COMP_5]

PERMEABILITY CALCULATION

ACT_PE[COMPS] = [0 ,
0 ,
0 ,
0 ,
0]

ADJ_PERM[COMP_1] = (2/(1+EFFLUX_ADJ[COMP_1]))*REGIONAL[COMP_1]*FLUX_ADJ[COMP_1]*3600+(CARRIER_DJ[COMP_1]*ACT_PE[COMP_1]*3600/(1+(CONCENTRATIONS[COMP_1]/(Km[COMP_1]))))*0

ADJ_PERM[COMP_2] = (2/(1+EFFLUX_ADJ[COMP_2]))*REGIONAL[COMP_2]*FLUX_ADJ[COMP_2]*3600+(CARRIER_DJ[COMP_2]*ACT_PE[COMP_2]*3600/(1+(CONCENTRATIONS[COMP_2]/(Km[COMP_2]))))

ADJ_PERM[COMP_3] = (2/(1+EFFLUX_ADJ[COMP_3]))*REGIONAL[COMP_3]*FLUX_ADJ[COMP_3]*3600+(CARRIER_DJ[COMP_3]*ACT_PE[COMP_3]*3600/(1+(CONCENTRATIONS[COMP_3]/(Km[COMP_3]))))

ADJ_PERM[COMP_4] = (2/(1+EFFLUX_ADJ[COMP_4]))*REGIONAL[COMP_4]*FLUX_ADJ[COMP_4]*3600+(CARRIER_DJ[COMP_4]*ACT_PE[COMP_4]*3600/(1+(CONCENTRATIONS[COMP_4]/(Km[COMP_4]))))

ADJ_PERM[COMP_5] = (2/(1+EFFLUX_ADJ[COMP_5]))*REGIONAL[COMP_5]*FLUX_ADJ[COMP_5]*3600+(CARRIER_DJ[COMP_5]*ACT_PE[COMP_5]*3600/(1+(CONCENTRATIONS[COMP_5]/(Km[COMP_5]))))

```
Km[COMPS] = [1 ,
1 ,
1 ,
1 ,
1 ]
PASS_PE[COMPS] = [0 ,
1.10E-06 ,
2.17E-06 ,
4.06E-06 ,
3.80E-06 ]
RC[COMP_1] = PASS_PE[COMP_1]*0
RC[COMP_2] = IF PASS_PE[COMP_2]>0 THEN 1 ELSE 0
RC[COMP_3] = IF PASS_PE[COMP_3]>0 THEN 2 ELSE 0
RC[COMP_4] = IF PASS_PE[COMP_4]>0 THEN 4 ELSE 0
RC[COMP_5] = PASS_PE[COMP_5]*0
RCSUM = RC[COMP_2]+RC[COMP_3]+RC[COMP_4]
REGIONAL[COMP_1] = PASS_PE[COMP_1]+RCSUM*0
REGIONAL[COMP_2] = if RCSUM=2 then
(EXP( -9.011926 + 2.594378 *LOGN(1/PASS_PE[COMP_2]) -0.065515
*LOGN(1/PASS_PE[COMP_2])^2))^(-1) else
if RCSUM=4 then

(EXP(-0.369414*LOGN(1/PASS_PE[COMP_4])+0.23756*LOGN(1/PASS_PE[COMP_4])^2-0.009
9719*LOGN(1/PASS_PE[COMP_4])^3))^(-1) else
if RCSUM=6 then
0.5*(EXP( -9.011926 + 2.594378 *LOGN(1/PASS_PE[COMP_3]) -0.065515
*LOGN(1/PASS_PE[COMP_3])^2))^(-1)
+0.5*(EXP( -21.009845 + 4.544238 *LOGN(1/PASS_PE[COMP_4]) -0.140815
*LOGN(1/PASS_PE[COMP_4])^2))^(-1) else
PASS_PE[COMP_2]
REGIONAL[COMP_3] = if RCSUM=1 then
(EXP( -3.238469 + 1.509131 *LOGN(1/PASS_PE[COMP_2]) -0.022109
*LOGN(1/PASS_PE[COMP_2])^2))^(-1) else
if RCSUM=4 then

(EXP(-0.093739*LOGN(1/PASS_PE[COMP_4])+0.182344*LOGN(1/PASS_PE[COMP_4])^2-0.00
23631*LOGN(1/PASS_PE[COMP_4])^3))^(-1) else
if RCSUM=5 then
0.5*(EXP( -3.238469 + 1.509131 *LOGN(1/PASS_PE[COMP_2]) -0.022109
*LOGN(1/PASS_PE[COMP_2])^2))^(-1)
+0.5*(EXP( -15.415683 + 3.543563 *LOGN(1/PASS_PE[COMP_4]) -0.100318
*LOGN(1/PASS_PE[COMP_4])^2))^(-1) else
PASS_PE[COMP_3]
```

```
REGIONAL[COMP_4] = if RCSUM=1 then
 (EXP( 14.455255 -1.264630 *LOGN(1/PASS_PE[COMP_2]) + 0.082015
 *LOGN(1/PASS_PE[COMP_2])^2))^(-1) else
 if RCSUM=2 then
 (EXP( 11.480333 -0.791109 *LOGN(1/PASS_PE[COMP_3]) + 0.066063
 *LOGN(1/PASS_PE[COMP_3])^2))^(-1) else
 if RCSUM=3 then
 0.5*(EXP( 14.455255 -1.264630 *LOGN(1/PASS_PE[COMP_2]) + 0.082015
 *LOGN(1/PASS_PE[COMP_2])^2))^(-1)
 +0.5*(EXP( 11.480333 -0.791109 *LOGN(1/PASS_PE[COMP_3]) + 0.066063
 *LOGN(1/PASS_PE[COMP_3])^2))^(-1) else
 PASS_PE[COMP_4]
REGIONAL[COMP_5] = PASS_PE[COMP_5] +RCSUM*0
SOLUBILIY CALCULATION
ADJ_SOLUB[COMP_1] = if USER_pH[COMP_1]>=pH[COMP_1] then USER_SOLUB[COMP_1]
 else
 ((USER_SOLUB[COMP_2]-USER_SOLUB[COMP_1])/(USER_pH[COMP_2]-USER_pH[COMP_1]
 ))*(pH[COMP_1]-USER_pH[COMP_1])+USER_SOLUB[COMP_1]
ADJ_SOLUB[COMP_2] = if USER_pH[COMP_2]=pH[COMP_2] then USER_SOLUB[COMP_2]
 else if USER_pH[COMP_2]<pH[COMP_2] then
 ((USER_SOLUB[COMP_3]-USER_SOLUB[COMP_2])/(USER_pH[COMP_3]-USER_pH[COMP_2]
 ))*(pH[COMP_2]-USER_pH[COMP_2])+USER_SOLUB[COMP_2] else
 ((USER_SOLUB[COMP_2]-USER_SOLUB[COMP_1])/(USER_pH[COMP_2]-USER_pH[COMP_1]
 ))*(pH[COMP_2]-USER_pH[COMP_1])+USER_SOLUB[COMP_1]
ADJ_SOLUB[COMP_3] = if USER_pH[COMP_3]=pH[COMP_3] then USER_SOLUB[COMP_3]
 else if USER_pH[COMP_3]<pH[COMP_3] then
 ((USER_SOLUB[COMP_4]-USER_SOLUB[COMP_3])/(USER_pH[COMP_4]-USER_pH[COMP_3]
 ))*(pH[COMP_3]-USER_pH[COMP_3])+USER_SOLUB[COMP_3] else
 ((USER_SOLUB[COMP_3]-USER_SOLUB[COMP_2])/(USER_pH[COMP_3]-USER_pH[COMP_2]
 ))*(pH[COMP_3]-USER_pH[COMP_2])+USER_SOLUB[COMP_2]
ADJ_SOLUB[COMP_4] = if USER_pH[COMP_4]=pH[COMP_4] then USER_SOLUB[COMP_4]
 else if USER_pH[COMP_4]<pH[COMP_4] then
 ((USER_SOLUB[COMP_5]-USER_SOLUB[COMP_4])/(USER_pH[COMP_5]-USER_pH[COMP_4]
 ))*(pH[COMP_4]-USER_pH[COMP_4])+USER_SOLUB[COMP_4] else
 ((USER_SOLUB[COMP_4]-USER_SOLUB[COMP_3])/(USER_pH[COMP_4]-USER_pH[COMP_3]
 ))*(pH[COMP_4]-USER_pH[COMP_3])+USER_SOLUB[COMP_3]
ADJ_SOLUB[COMP_5] = if USER_pH[COMP_3]=pH[COMP_3] then USER_SOLUB[COMP_3]
 else if USER_pH[COMP_3]<pH[COMP_3] then
 ((USER_SOLUB[COMP_4]-USER_SOLUB[COMP_3])/(USER_pH[COMP_4]-USER_pH[COMP_3]
 ))*(pH[COMP_3]-USER_pH[COMP_3])+USER_SOLUB[COMP_3] else
 ((USER_SOLUB[COMP_3]-USER_SOLUB[COMP_2])/(USER_pH[COMP_3]-USER_pH[COMP_2]
 ))*(pH[COMP_3]-USER_pH[COMP_2])+USER_SOLUB[COMP_2]
USER_pH[COMPS] = [1.5 ,
 5 ,
 6.5 ,
 7 ,
 7.5 ]
```

```
USER_SOLUB[COMPS] = [31 ,
3.65 ,
3.65 ,
3.65 ,
3.65 ]
TRANSIT TIME
ADJ_TRANSIT_TIME[COMP_1] = .5*TRANSIT_ADJ[COMP_1]*USER_TT_INPUT
ADJ_TRANSIT_TIME[COMP_2] = .25*TRANSIT_ADJ[COMP_2]*USER_TT_INPUT
ADJ_TRANSIT_TIME[COMP_3] = 1.5*TRANSIT_ADJ[COMP_3]*USER_TT_INPUT
ADJ_TRANSIT_TIME[COMP_4] = 1.5*TRANSIT_ADJ[COMP_4]*USER_TT_INPUT
ADJ_TRANSIT_TIME[COMP_5] = 24*TRANSIT_ADJ[COMP_5]*USER_TT_INPUT
CUMU_TT[COMP_1] = ADJ_TRANSIT_TIME[COMP_1]
CUMU_TT[COMP_2] = ADJ_TRANSIT_TIME[COMP_1]+ADJ_TRANSIT_TIME[COMP_2]
CUMU_TT[COMP_3] =
ADJ_TRANSIT_TIME[COMP_1]+ADJ_TRANSIT_TIME[COMP_2]+ADJ_TRANSIT_TIME[COMP_
3]
CUMU_TT[COMP_4] =
ADJ_TRANSIT_TIME[COMP_1]+ADJ_TRANSIT_TIME[COMP_2]+ADJ_TRANSIT_TIME[COMP_
3]+ADJ_TRANSIT_TIME[COMP_4]
CUMU_TT[COMP_5] =
ADJ_TRANSIT_TIME[COMP_1]+ADJ_TRANSIT_TIME[COMP_2]+ADJ_TRANSIT_TIME[COMP_
3]+ADJ_TRANSIT_TIME[COMP_4]+ADJ_TRANSIT_TIME[COMP_5]
TRANSFERS[COMP_1] = LOGN(10)/ADJ_TRANSIT_TIME[COMP_1]
TRANSFERS[COMP_2] = LOGN(10)/ADJ_TRANSIT_TIME[COMP_2]
TRANSFERS[COMP_3] = LOGN(10)/ADJ_TRANSIT_TIME[COMP_3]
TRANSFERS[COMP_4] = LOGN(10)/ADJ_TRANSIT_TIME[COMP_4]
TRANSFERS[COMP_5] = LOGN(10)/ADJ_TRANSIT_TIME[COMP_5]
USER_TT_INPUT = 1
```